Published in final edited form as:
Maturitas. 2010 September ; 67(1): 34–38. doi:10.1016/j.maturitas.2010.04.016.

The Neuroendocrine physiology of female reproductive aging: an update

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Abstract

The transition into menopause is a complex process that affects fertility and increases the risk for a number of health problems in aging women that include, but are not limited to osteoporosis, heart disease, diabetes mellitus and cognitive dysfunction. Improved nutrition and enhanced access to medical care have increased the average lifespan for women in developed countries, and many will spend more than one third of their life in a post-menopausal state. Epidemiological studies indicate that a delayed natural menopause confers longevity and decelerates the appearance of much age-related morbidity, suggesting that developing treatments to delay menopause would significantly improve quality of life for women. Although menopause is ultimately defined by ovarian follicular exhaustion, several lines of scientific evidence in humans and animals now suggest that dysregulation of estradiol feedback mechanisms and hypothalamic-pituitary dysfunction contributes to the onset and progression of reproductive senescence, independent of ovarian failure. This article provides a brief update on our current understanding of the role of the hypothalamic-pituitary axis in the onset of and transition into female reproductive senescence.

Keywords

Female; Reproduction; Menopause; Senescence; Neuroendocrine

Introduction

Female reproductive senescence is a lifelong process that begins before birth and culminates with ovarian follicular depletion and the menopause. For many years, the menopausal transition was viewed to be simply the end product of accelerated oocyte depletion. Moreover, hypothalamic-pituitary axis (HPA) dysfunction was thought to reflect a compensatory response to the gradual decline in the number and quality of remaining oocytes. However, recent studies challenge the conventional belief that ovarian aging is the sole determinant of when females begin the transition into reproductive senescence and raise

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questions about the sequence of pathophysiological events that initiate reproductive quiescence.[1] There is now a convincing body of literature in primates and non-primates that support a role for HPA dysfunction independent of ovarian aging in the transition into reproductive senescence.[1,2] Moreover, aberrant responsiveness of the HPA to estrogen feedback and the subsequent generation of abnormal patterns of gonadotropin release may in itself accelerate ovarian follicular exhaustion.[3] Defining the physiological and cellular mechanisms that initiate female reproductive senescence is an area of intense scientific interest. Understanding the mechanisms that propel women into the menopause may offer opportunities for interventions that delay menopause-related increases in disease morbidity and thus improve the overall quality of life for aging women. This article focuses on our current understanding of the role of HPA dysfunction in the transition into female reproductive senescence.

NONHUMAN MODELS OF FEMALE REPRODUCTIVE AGING AND THE HPA

Induction of the LH surge

Estrogen receptor α (ESR1) mediates estradiol negative and positive feedback, the latter leading to the high amplitude preovulatory LH surge. Although hypothalamic GnRH neurons orchestrate pituitary gonadotropin release, they do not express ESR1. Therefore, estradiol likely exerts positive feedback onto GnRH neurons by modulating afferent inputs from estrogen-responsive, ESR1-expressing neurons. Consistent with this hypothesis, GnRH neurons receive synaptic input from a variety of neurotransmitter systems that are modulated by estradiol and that either excite or inhibit GnRH neurons. Estradiol-mediated changes in the balance between excitatory and inhibitory neurotransmission onto GnRH neurons are thought to underlie the generation of the LH surge.

GnRH neurons receive input from a number of neurotransmitter pathways however glutamate, GABA, norepinenphrine and kisspeptin are identified as the key neurotransmitters involved in the generation of the LH surge. Release of the excitatory amino acid glutamate[14–16] and the excitatory peptide kisspeptin[17,18] on the day of the LH surge are regulated by estradiol and hypothesized to be critical to LH surge induction. Consistent with this hypothesis, glutamate receptor antagonists or kisspeptin immunoneutralization attenuate GnRH release and block the LH surge[18–20]. Norepinephrine[21,22] and vasoactive intestinal peptide (VIP)[23,24] also facilitate induction of normal LH surges. In contrast, the inhibitory neurotransmitter GABA attenuates LH release under estradiol negative feedback conditions[25], and reduced GABA neurotransmission in the hypothalamus may be required for the induction of a high amplitude LH surge[26–29].

RODENTS

Rodents are useful models for studying female reproductive physiology because they exhibit a high degree of genetic and physiologic similarity to humans, have a relatively short life span, and homogeneous strains are widely available at low cost.[4] The rodent estrous cycle exhibits similar patterns of cyclic changes in serum LH, FSH, estradiol and progesterone levels as the human menstrual cycle. The primary differences are the very short luteal phase and the absence of menses when pregnancy does not occur in rodents. Although reproductive aging manifests somewhat differently in rodents and humans (e.g., oocyte depletion does not occur before rodents become reproductively senescent),[5] several fundamental similarities are seen in perimenopausal women and middle-aged rodents: 1) one of the first physiological signs of impending reproductive senescence is elevated FSH levels;[6–10] 2) elevated FSH is associated with attenuated granulosa cell production of inhibin B; 3) middle-aged rats[8] and women[11] exhibit altered hypothalamic-pituitary axis responsiveness to estrogen positive feedback; 4) altered patterns of gonadotropin secretion occur long

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before overt ovarian failure[8,11]; and 5) both humans and rodents develop highly variable cycle lengths with erratic ovarian steroid production preceding reproductive quiescence.[5] Because so many changes in reproductively aging rodents parallel those in aging women,[1,12] we and other investigators have used female rodents, especially rats, to explore the role of the HPA in the onset of female reproductive senescence. Consequently, much of what we know about the HPA and female reproductive aging is derived from studies in rats.[13]

The first clue that the HPA is involved in female reproductive aging

Studies pioneered by the endocrinologist Selmar Aschheim in 1964 showed that ovaries transplanted from young female rats with normal estrous cycles into old, non-cycling mice failed to restore estrous cyclicity, suggesting that the ovary is not the sole determinant of female reproductive senescence.[30] In 1972, Peng and Huang reported that ovaries harvested from old mice and transplanted into young ovariectomized mice supported normal estrous cycles and formed corpora lutea, whereas hypothalamic transplants from old mice into young, ovary intact females did not.[31] These were the first studies to demonstrate clearly that exhaustion of ovarian gametes is not the exclusive determinant of female reproductive senescence.

There is now substantial evidence that age–related ovarian failure is preceded by abnormal responsiveness of the neuroendocrine axis to estrogen positive feedback. For example middle-aged, eugonadal rats demonstrate increased FSH and delayed and attenuated LH surges despite normal estrous cycle lengths.[32] Changes in the positive feedback effects of estradiol on the LH surge in regularly cycling, middle-aged rats are not due to altered ovarian steroid exposure[15,33], primary pituitary dysfunction[34,35], or reduced ESR1 or progestin receptor expression and/or binding in the hypothalamus[36–38] or the pituitary[39,40]. Instead, available data overwhelmingly support impaired hypothalamic responses to estradiol positive feedback as the etiology of alterations in LH release in reproductively aging rodents.[13] LH surge abnormalities can subsequently affect ovarian physiology and increase rates of folliculogenesis, which may accelerate ovarian follicular depletion.[4]

GnRH neurons and aging

Notably age-related LH surge dysfunction is not attributable to reduced numbers or abnormal morphology of GnRH neurons[33,41–43]. Push-pull perfusion measurements of *in vivo* GnRH output from the mediobasal hypothalamus of middle-aged rats suggest that GnRH peptide release is attenuated[44] under estradiol positive feedback conditions, even though GnRH peptide content is unchanged or increased[35]. Moreover, GnRH mRNA[45] may decrease, and fewer GnRH neurons express cFos[33,46], a marker for GnRH neuron activation, in middle-aged compared to young rats. Because hypothalamic fragments from young and middle-aged rats release similar amounts of GnRH peptide in response to potassium depolarization[47], the data suggest that decreased preovulatory GnRH release most likely reflects impaired GnRH neuronal activation under estrogen positive feedback conditions.[5]

Excitatory and inhibitory neurotransmission and female reproductive aging

Estradiol negative feedback remains intact in middle-aged rats.[15] In contrast female reproductive senescence in rodents is associated with a reduced ability of the HPA to respond to estradiol positive feedback conditions.[8,32] There is now good evidence that middle-aged rats do not respond to estradiol positive feedback with appropriate modulation of excitatory and inhibitory hypothalamic neurotransmitter release[28,34,48,2,23,28,34,46]. This in turn could cause reduced activation of GnRH neurons, reduced GnRH release, and an abnormal LH surge[23,46]. GnRH neurons from middle-aged rats receive reduced input from the excitatory neurotransmitters glutamate[14] and norepinephrine[49] and the excitatory neuropeptide kisspeptin and increased inhibitory input from the neurotransmitter GABA.

[28,34,50] Restoration of excitatory neurotransmission, either by increasing glutamate and kisspeptin (excitatory) or decreasing GABA (inhibitory) rescues LH surge amplitude in middle-aged rats.[28,34] Middle-aged rats may also be less responsive to excitatory input[28,51], perhaps in part reflecting changes in glutamate receptor stoichiometry on GnRH neurons[52] and terminals[53]. Other modulators of GnRH release also change in middle-aged rats exhibiting delayed and attenuated LH surges. Examples include norepinephrine,[54,55] neuropeptide Y,[56] and VIP.[24] Interestingly GABA modulates norepiniephrine[57] and glutamate[28] release; hence, increased hypothalamic GABA release may restrain excitatory signals transmitted by these neurotransmitters to GnRH neurons. Insulin-like growth factor -1 (IGF-1) is also reduced in the brains of middle-aged rats.[45] We have found that intracerebral infusion of IGF-1 partially rescues the LH surge in middle-aged rats.[35] IGF-1 signaling, presumably in the hypothalamus, is necessary for estradiol positive feedback and may modulate the synthesis or release of kisspeptin or VIP and/or the expression of glutamate receptors[58,59]. Thus, it is possible that reduced hypothalamic IGF-1 indirectly affects GnRH neuron activity by disrupting excitatory inputs mediated by glutamate and kisspeptin[60–62].

NONHUMAN PRIMATES

Nonhuman primate studies that focus on the role of the neuroendocrine axis in female reproductive aging are limited because of the high cost and facilities required to maintain and age captive colonies. Nonetheless, several studies suggest that reproductively aging *Macaca mulatta* exhibit hormonal profiles consistent with those observed in reproductively aging women. For example, the transition into reproductive senescence is heralded by increased menstrual cycle irregularity, elevated FSH, decreased inhibin B and antimullerian hormone (AMH), and diminished ovarian reserve[64,65]. Additionally, hypothalamic push-pull perfusion studies of GnRH peptide pulsatility and release suggest that when compared to young reproductive aged females, older reproductive aged nonhuman female primates exhibit an increase in the mean concentration of GnRH pulses without changing GnRH pulse frequency [66]. Collectively, these studies suggest that reproductive aging in nonhuman primates parallels human aging and that additional studies using nonhuman primates can provide highly relevant information about female reproductive senescence and the neuroendocrine axis dysfunction.

THE ROLE OF THE HPA AXIS IN HUMAN FEMALE REPRODUCTIVE SENESCENCE

Female reproductive senescence in humans is remarkably similar to that in aging female rodents. Like rodents, ovarian steroid negative feedback remains intact in elderly women.[67] Additionally a study by Klein et al.[3] of 12 young (20–24 years old) and 18 middle-aged (40–45 years old), regularly cycling women demonstrated that middle-aged women had significantly higher FSH levels despite having equivalent levels of estradiol, progesterone and inhibin B. This resulted in shortened follicular stages and accelerated follicular development and depletion. These data not only imply that neuroendocrine dysfunction in reproductively aging women develops independently of overt ovarian dysfunction, but that neuroendocrine dysfunction may increase the rate of ovarian follicular depletion. Like rodents, perimenopausal women exhibit neuroendocrine dysfunction characterized by failure of estrogen positive feedback conditions to induce a LH surge. A recent longitudinal study of 13 healthy women aged 45–47 making the transition into the menopause suggested that perimenopausal women exhibit a wide spectrum of reproductive phenotypes which are characterized by normal, attenuated, and failed LH surge induction under estradiol positive feedback conditions. A small study of 5 perimenopausal women with a history of dysfunctional uterine bleeding also demonstrated a failure of estrogen positive feedback conditions to induce a LH surge in 3/5 perimenopausal women compared to all young reproductive aged women[68]. Additionally a subset of study participants enrolled in the multiethnic observational cohort Study of Women across the Nation (SWAN), in which urine samples were collected daily for determination of urinary levels of estrone conjugates, pregnane-3-diol (estrogen and progesterone metabolites, respectively), LH, and FSH showed that there is a frequent failure of estrogen positive feedback conditions to induce an appropriately timed, high amplitude LH surge in some perimenopausal women.[11] In another study of 8 young (25–33 years) and 8 perimenopausal women (45–50 years), researchers administered early follicular phase estradiol boluses to induce an LH surge. Three-fourths of the young women but only one of perimenopausal woman responded to the estradiol bolus with an LH surge.[69] Collectively, all of these studies are consistent with the hypothesis that there is disruption in estrogen regulation of the hypothalamic-pituitary axis.

Female reproductive senescence is not associated with an age-related loss of GnRH neurons.[70] Human and nonhuman studies suggest that neuroendocrine dysfunction in the early menopause may reflect alterations in hypothalamic kisspeptin neurotransmission[71]. We assessed the effect of reproductive age on pituitary responsiveness to GnRH by comparing LH and FSH release in young and perimenopausal women primed with estradiol and progesterone and challenged with graded GnRH pulses. We found perimenopausal women have a similar if not more robust response to GnRH challenge than young women (unpublished observations). Our studies suggest that it is unlikely that neuroendocrine dysfunction during the menopausal transition reflects age-related pituitary dysfunction. Nonetheless despite evidence of normal pituitary function and unchanged numbers of GnRH neurons, middle-aged women continue exhibit abnormal responsiveness to estradiol positive feedback conditions, which manifests as attenuated LH release[10] and irregular LH surge patterns.[11]

One recent study that monitored serum gonadal steroids and gonadotropins in 21 mid-reproductive aged women and 56 perimenopausal to early menopausal women aged 45 to 55 (categorized into three groups according to the menstrual cycle criteria Stages of Reproductive Aging Workshop[72]) suggested that aberrant estradiol secretion patterns (luteal follicular phase-like rise in estradiol) also referred to as a luteal out of phase (LOOP) follicular event, might explain the increased frequency of menstrual cycle irregularities during the menopausal transition[73]. The authors hypothesize that these LOOP events reflect ovarian dysfunction characterized by an early ovulatory event in the mid-to-late luteal phase which then causes an abnormally short or long menstrual cycle length.

Young and older menopausal women are different

Although there is good evidence that the menopausal transition involves changes in the responsiveness of the neuroendocrine axis to ovarian steroids, it is important to note that perimenopausal and early menopausal females do not respond to gonadal steroid feedback or GnRH challenges like advanced reproductive aged women. A more recent study showed that when challenged with graded doses of GnRH, young menopausal women (52.9±0.8 years old) release more LH and FSH than older menopausal women (72.8±0.8 years old).[74] Additionally, older menopausal women exhibit decreased GnRH pulse frequencies but an increase in overall GnRH secretion when compared to younger menopausal women[67,75,76]. These findings clearly suggest that the number of years postmenopause may profoundly affect the responsiveness of the HPA to endogenous and exogenous modulators. Thus, analysis of the duration of reproductive quiescence (i.e. time since menopause) should be incorporated in studies attempting to unravel mechanisms underlying multiorgan system morbidity in chronologically aging women.

Conclusion

Female reproductive senescence is a complex process that adversely affects a number of organ systems and negatively influences overall health status and quality of life in aging women. Accelerated ovarian follicular depletion is a hallmark of reproductive aging; however, studies in primates and non-primates support an independent role for the HPA in the initiation of reproductive senescence. Understanding the differential roles of the ovaries and the HPA in the transition into the menopause may provide a foundation for the development of interventions that delay menopause-related increases in morbidity and thus improve the overall quality of life for aging women.

Acknowledgments

We would like to thank Drs. Anne Etgen and Lubna Pal for their thoughtful comments during the preparation of this manuscript.

Grant support: Supported by Robert Wood Johnson Foundation, American Federation for Aging and the Albert Einstein College of Medicine. This research was also supported by the Eunice Kennedy Shriver NICHD/NIH through cooperative agreement HD058155 as part of the Specialized Cooperative Centers Program in Reproduction and Infertility Research.

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